mucous membrane of the mammal a preparation comprising transfersomes. Support for these claims found throughout the specification and in previously filed claims 1, 3-13, 15-21 and 34-48. Support for claim 62 is found on page 21, line 19 et seq. of the specification. No new matter has been added. The new claims which include the Markush groups previously objected to by the Examiner have been carefully revised in order to remove alternative language terms.

Rejection Under 35 U.S.C. §112, Second Paragraph

New claims 53-90, track now cancelled claims 1, 3-13, 15-21 and 34-48, but have been revised to method of treatment. It is respectfully submitted that the informalities identified in the Office Action of April 20, 2001 with respect to the now-cancelled claims are not present in new claims 53-84, and that these new claims are in full compliance with 35 U.S.C.§ 112, second paragraph.

Rejection Under 35 U.S.C. §102

In the Office Action, claims 1 and 3-52 were rejected under 35 U.S.C. §102(b) anticipated by EP 0220 797 to Nikko Chemicals Co. Ltd., (Nikko) or U.S. Patent No. 4,921,706 to Roberts, (Roberts), Mayer (BBA, 1986), Blume (J. Of Liposome Research, 1992), EP 707 847 (Bayer) or EP 704 0 206 (Regenold). The Examiner stated the EP 797 "discloses liposomes containing a drug, an amphiphilic lipid and a surfactant in instant amounts and a method of preparation." The Examiner further stated that Roberts, Mayer, EP 847 and EP 206 similarly "all teach liposomes containing an amphiphilic lipid and a method of preparation" and stated that Blume and EP 160 "teach transfersomes and a method of preparation."

The Examiner concludes that "the methodology used in the preparation of instant compositions is the same as the classical method of preparation of liposomes using one or more amphipathic lipids...The examiner is unable to determine the differences between instant composition and those in EP references cited since there are no translations."

It is noted that the Examiner's comment concerning EP references lacking translations is believed to be limited to EP 0 707 847 (Bayer), EP 0 704 206 (Renenold), and EP 0 475 160 (Cevc). Each of these references have corresponding U.S. patents, which are being made of record in the concurrently filed IDS, and copies of which are supplied herewith. Specifically, U.S. patent 5,541,515 corresponds to EP 0 707 847 (Bayer); U.S. Patent No. 5,958,379 corresponds to EP 0 704 206 (Renenold); and U.S. patent No. 6,165,500 corresponds to EP 0 475 160 (Cevc).

There are important differences between the descriptions provided in the above references relied upon by the Examiner and the presently claimed invention. First of all, the claims of the invention are directed to a method of manufacture of, and a method of treatment using, a preparation for the transport of at least one active agent through the skin or mucous membrane of the mammal, which preparation comprises transfersomes which are suspended in a pharmaceutically acceptable medium for application onto the skin or mucous membrane of a mammal. The term "transfersome" itself is known to those of ordinary skill in the art to represent something different than a liposome, even though the components thereof and general method of manufacture are similar. The transfersomes of the present invention comprise liquid droplets encompassed within a sheath comprising at least two amphiphilic lipid components which differ in their solubility in the pharmaceutical acceptable medium by a factor of at least 10, the two amphiphilic compounds being selected such that the transfersomes are capable of undergoing sufficient deformation to pass through the skin or mucous membrane without being solubilized. Transfersomes are much larger than conventional Micelle-like carrier formulations and are subject to different diffusion laws, for example, the permeability of transfersomes is not a linear function of the driving pressure, as it is in the case of liposomes.

In the case of transfersomes, the permeability increases disproportionately or nonlinearly as the pressure increases (see: specification page 5, first paragraph); ii) substances introduced through constrictions by means of transfersomes, can develop in man almost 100% of the maximum obtainable biological or therapeutic potential (see: specification page 5, first

paragraph); iii) the transfersomes either do not have a solubilization point or are far removed from the solubilization point and permit the rapid and effective transport of active ingredients through barriers and constrictions (see: specification page 6, first paragraph).

None of the references relied upon by the Examiner disclose preparing such transfersomes, nor do they disclose a method of treatment utilizing such transfersomes.

It is respectfully submitted that the liposomes described in the EP '797 reference will not act in accordance with the transfersomes of the present invention. The liposomes exemplified in the EP '797 reference include stabilizers, which tend to strengthen the liposomes, or reduce their deformability. This is in contrast to the presently claimed transfersomes, which are highly deformable so that they pass through the skin or mucous membrane without being solubilized, thereby carrying the active agent with them. In this regard, a Declaration of the inventor, Professor Gregor Cevc, is enclosed herewith, which distinguishes transfersomes and liposomes demonstrates that liposomes made in accordance with the EP '797 reference (e.g., Example 1) are not able to pass through a filter (an Anapore membrane with 20 mm pores).

In view of the particular combination of amphiphilic lipid components recited in the claims which lead to the different properties specifically recited in the claims between the transfersomes of the presently claimed methods and the liposomes which may be prepared following the directions of the EP '797 reference, it is respectfully submitted that EP '797 does not anticipate the claims as presented herein.

The '706 reference to Roberts relates to unilamellar lipid vesicles comprised of short-chain phospholipids and long-chain phospholipids and a method for making the same. While the '706 reference generally states that the vesicles produced by the method describing the '706 reference can be used for delivery of drugs, it neither teaches nor suggests a method of treatment of a mammal with a preparation for the transport of at least one active agent by administering the preparation comprising the transfersomes of the invention to the skin or mucous membrane of

the mammal, such that the two amphiphilic lipid compounds form transfersomes capable of undergoing sufficient deformation to pass through the skin or mucous membrane without being solubilized. Nor does Roberts direct one to choose at least two amphiphilic lipid components which differ in their solubility in the pharmaceutical acceptable medium by a factor of at least 10, the two amphiphilic compounds being selected such that the transfersomes are capable of undergoing sufficient deformation to pass through the skin or mucous membrane without being solubilized. Accordingly, it is respectfully submitted that Roberts does not anticipate the claims as presented herein.

The reference to Mayer describes unilamellar or plurilamellar vesicles produced by utilizing filters with pore sizes from 30 to 400 nm. Mayer does not describe a method of treatment whatsoever and especially not a method of treatment by administering to the skin or mucous membrane of a mammal a preparation comprising the transfersomes of the present invention. To the extent that Mayer does not even contemplate the inclusion of an active agent, Mayer cannot anticipate the present claims.

The Blume reference describes lipid vesicles composed of phosphatidylcholine and suitable polyoxyethylene derivative of phosphatidylethanolamine to obtain cryptosomes, a type of liposome. While the liposomes described in Blume can be used as drugs carriers when injected in vivo in mice experiments, there is no disclosure whatsoever of administering to the skin or mucous membrane of a mammal the transfersomes having the characteristics recited in claim 1. There is no disclosure of transfersomes in Blume. Blume cannot anticipate the present claims.

EP 0 707 847 (and corresponding U.S. Patent No. 5,741,515) describes the preparation of ketoprofen liposomes for topical applications. The ketoprofen liposomes gels described in Bayer are prepared by incorporating ketoprofen phospholipid micelles in certain hydrogels. See, column 3, line 55 et seq. There is neither a disclosure nor suggestion whatsoever in Bayer of a method of treatment of a mammal with the preparation that comprises transfersomes having the

characteristics claimed in claim 1, wherein the two amphiphilic lipid components differ in their solubility by a factor of at least 10, such that the transfersomes are capable of undergoing sufficient deformation to pass through the skin or mucous membrane without being solubilized. Moreover, there is no disclosure whatsoever that the permeation capability relative to reference particles of water is between 10^{-5} to 1 as claimed in claim 59. Therefore, this reference cannot anticipate the present claims.

EP 0 704 206 (and corresponding U.S. Patent No. 5,958,379 to Regenold et al.) discloses a pharmaceutical composition containing an active substance that can be sprayed on skin or mucous membrane. Upon spraying the composition of Regenold on the skin, a preparation is formed which has a higher concentration of the active substance than that of the originally sprayed pharmaceutical composition. In column 8, line 15 et seq. Regenold further describes a composition that is a dispersion containing liposomes and an active substance such that upon spraying, the active substance and not the liposome is transported through the skin barrier or deposited on the body surface. Regenold clearly neither teaches nor suggests a method of treatment of a mammal comprised of administering transfersomes having the specific properties claimed in claim 1, i.e., they are capable of undergoing sufficient deformation to pass through the skin or mucous membrane without being solubilized. Therefore, this reference cannot anticipate the present claims.

Although the Examiner mentions "EP 106" (EP 0 475 160) in his discussion of Blume, it is not clear whether the Examiner was relying on this reference as a separate basis for anticipation of the claims. EP 0 475 160 corresponds to the Inventor's U.S. Patent No. 6,165,500. In any event, EP 106 was cited by the European Examiner in the International Search Report as defining the general state of the art and which is not considered to be of particular relevance to the present invention.

Accordingly, it is respectfully submitted that the rejections under 35 USC § 102 have been obviated and should be removed.

Rejection Under 35 U.S.C. § 103

In the Office Action the Examiner rejected claims 1 and 3-52 under 35 U.S.C. § 103(a) on the grounds of being unpatentable over the references cited above with respect to the § 102 rejections. The Examiner stated that, although "the references teach liposomes or transfersomes containing a drug an amphiphilic lipid and a surfactant in instant amounts and a method of preparation", "[i]t is unclear whether the references teach all of the instant functional parameters. In case they are different, in the absence of showing the criticality, they are deemed to be parameters manipulated by an artisan to obtain the best possible results." This statement in of itself is respectfully submitted to be an acknowledgement by the Examiner that one skilled in the art would not, without the improper use of hindsight and manipulation of these disclosures, be able to construct the presently claimed invention from these references. Accordingly, Applicant respectfully traverses this rejection. It is respectfully submitted that none of the cited references either discloses or suggests preparing transfersomes which undergo sufficient deformation to transport on active agent through skin or mucous membranes due to the selection of at least two amphiphilic lipid components that differ in their solubility in the transfersome medium by a factor of at least 10. Furthermore, none of these references teaches or suggests the claimed method of treatment with transfersomes carrying an active agent that undergo sufficient deformation to transport through skin or mucous membranes without being solubilized.

The Examiner takes the position that, absent a showing of criticality, these parameters would be manipulable by one skilled in the art in order to arrive at the present invention. However, the claims themselves set forth the very criticality that the Examiner is seeking, i.e., the requirement that the transfersomes are comprised of at least two amphiphilic lipid components that differ in their solubility in the transfersome medium by a factor of at least 10, in order to provide transfersomes which undergo sufficient deformation to transport through skin or mucous membranes. It is further respectfully submitted that the Examples set forth in the disclosure, along with the comparative examples and discussion concerning the same, provide the showing of criticality requested by the Examiner. In particular, the specification of the present invention provides ample evidence that the preparations of the prior art do not perform as (i.e., their permeation capability is significantly less than that of) the claimed invention. On page 31, lines 10 and 11, pages 40-41 and in Figures 3 and 8 of the subject application, Applicant has shown

that the permeation capability of liposomes (including the liposomes of EP '797) is lower than that of Applicant's transfersomes. Further, the Examiner's attention is respectfully directed to page 32 of the specification, wherein the carrier permeation capability of Examples 5-6 is compared to prior art liposome preparations. It is stated therein, and shown in Figure 4 of the specification, that the transfersomes of the subject invention formed from SPC and didecanoyl phosphatidyl choline have a higher permeation capability than do the liposomes formed from pure SPC.

Further, included in the specification at pages 38-41 are Comparison Examples A to E which are directed to formulations described in the prior art. Comparison Example D is actually Example 4 of EP 0220 797, relied upon by the Examiner (see page 40 of the specification). At page 41 of the specification, Applicant stated:

> In Figure 8, the permeation capability (at a constant pressure of 0.9 MPa) is shown for the Comparison Examples A to E and for an inventive ibuprofen/SPS transfersome in the form of a bar graph. It is clearly evident from the bar graph (Figure 8) that, at an elevated pressure (0.9 MPa), the permeation capability of the compositions of the Comparison Examples A to E ***is significantly less than that of the inventive transfersomes.***(Emphasis added).

Therefore, Applicant has already demonstrated the advantageous results obtained by the claimed preparations and methods, contrary to the Examiner's assertion.

The above arguments regarding the permeation capability of the transfersomes apply equally to methods of treatment with the transfersomes of the present invention.

Accordingly, Applicant respectfully submits that the rejections under 35 U.S.C. §103 have been obviated and should be removed.

Conclusion

It is respectfully submitted that the rejections in the previous Office Action have been obviated and should be withdrawn. Applicant respectfully submits that the pending claims are now in condition for allowance. Should there be any outstanding issues remaining, the Examiner is urged to contact the undersigned at the telephone number provided below. An early and

favorable action on the merits is earnestly solicited

Respectfully submitted,

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